## REMARKS

Claims 1, 11, 12, 14, 20, 30, and 41 are amended and claims 13, 15, 21-27, and 32-40 are canceled. Therefore, the claims pending in the Application are claims 1-12, 14, 16-20, 28-31, 41-42 and 45-47. No new matter has been added. Applicant reserves the right to pursue any canceled subject matter in future applications that claim priority to the present application.

As a general matter, Applicant amends claim 1 to recite "a therapeutically effective amount of a compound for ***inhibiting*** tumor metastasis..." rather than "a therapeutically effective amount of a compound for ***treating*** tumor metastases..." (emphasis added). Support for this amendment can be found at least in paragraph [0263] of the present specification.

### I. Rejection under 35 U.S.C. §112, para. 1

Claims 1-12, 14, 16-20, 27, 30, 41-42, and 45-47 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner acknowledges that the use of a compound of Formula I for treating tumor metastases is enabled but appears to object to the scope of the compounds claimed on the ground that:

> "[...] the specification, while being enabling for the compounds identified as having activity ***through relevant experimental data***, does not reasonably provide enablement for the asserted utility of the entirety of the claim scope, in particular for treating tumor metastases. The specification does not enable a person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
>
> Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of treating tumors with pharmaceuticals." (emphasis added)

Thus, the Examiner seems to be taking the position that the specification is enabling ***only*** with respect to compounds for which data are provided. This is not the legal standard, nor should it be.

Moreover, Applicant respectfully submits that the Examiner has overlooked significant enablement provided by the specification demonstrating effective biological activity of compounds of the claimed compositions for inhibiting tumor metastasis. The Examiner asserts (at page 5 of the Office Action) that Applicant provides data for what appears to be only 3

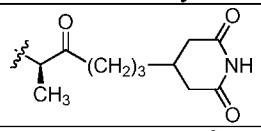
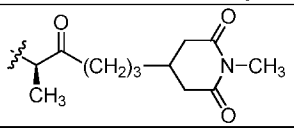
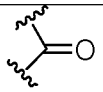
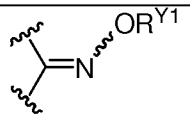
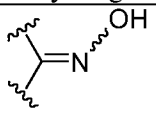
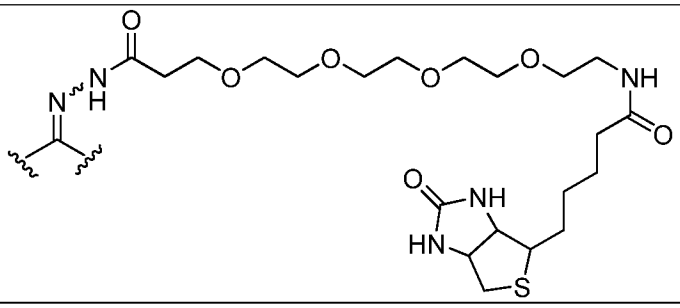
compounds when considering the "Number of Working Examples and Guidance Provided by Applicant." The Examiner is incorrect.

The present specification includes a variety relevant biological data including, for example: (1) tube formation assays (3 compounds; see for example Table 1, paragraph [0329]); (2) chamber cell migration assays (16 compounds; see for example Tables 4-6, paragraphs [0397]-[0402]); and (3) in vivo mouse breast cancer model studies (2 compounds, see for example paragraphs [0336], Example 57, and Figure 4). One of skill in the art would recognize that tube formation assays are assays commonly used to investigating angiogenesis (*i.e.,* the generation of new blood vessels) and would appreciate that inhibiting angiogenesis at a tumor cite would inhibit the generation of new blood vessels to the tumor and thus necessarily preclude metastasis by way of newly formed blood vessels to other parts of the body. Similarly, chamber cell migration assays (using, *e.g.,* 4T1 mouse breast tumor cells) are known in the art and are routinely used as a model for, *inter alia*, human breast cancer because the spread of cells can be seen to mimic metastasis of human mammary cancer (see paragraph [0333], page 143). Likewise, *in vivo* mouse breast cancer model studies are well known in the art and were conducted here in order to validate the *in vitro* findings as good predictors or therapeutic activity *in vivo* (see paragraph [0336], page 144).

In view of the above, Applicant submits that relevant biological data are explicitly provided for compounds having the following functional groups set out in **Table 1**, below, and that even by the Examiner's overly stringent standard, claims reciting these groups (*i.e.,* claim 1, claim 11, *etc.*, and claims depending therefrom) are clearly enabled.

**Table 1**

| Variable | Definition | Moiety (Tested Compound*) |
|---|---|---|
| $R^1$ | hydrogen | (all) |
| $R^2$ | hydrogen | (all) |
| $R^3$ | lower alkyl | methyl (all) |
| $R^4$ | $-OR^{4A}$ | -OH (1, 41, 42, 45, 48, 51, 55, 60, 65, 68-73, n-methylmigrastatin) |
| | oxo | (50) |
| | $-OC(=O)R^{4A}$ | $-O(CO)CH_3$ (49) |
| $R^{4A}$ | hydrogen | - |
| | lower alkyl | $-CH_3$ (49) |

| | | |
|---|---|---|
| | O-protecting group | TBS (37) |
| $R^5$ | lower alkyl | $-CH_3$ (all) |
| $R^6$ | lower alkyl | $-CH_3$ (all) |
| $X_1$ (X1/X2 = H) | O | (41, 42, 45, 48-51, 65, 68, n-methylmigrastatin) |
| | $NR^{X1}$ | -NH (55) |
| | $CR^{X1}R^{X2}$ | $-CH_2$ (60, 69-73) |
| Q | hydrogen | (45, 48-51, 55, 60, 69-72) |
| | lower alkyl | i-Pr (65, 68) |
| |  | (1, 41) |
| |  | (42, n-methylmigrastatin) |
| $Y_1/Y_2$ | hydrogen | (69) |
| | lower alkyl | $-CH_3$ (70) |
| | $CF_3$ | (71) |
| | $WR^{Y1}$ | -OH (69-71) |
| |  | (41, 42, 45, 48-51, 55, 60, 65, 68, n-methylmigrastatin) |
| |  |  (72) |
| |  | (73) |
| $R^{Y1}$ | hydrogen | - |
| | lower alkyl | - |
| | heteroaliphatic | biotinylated (73) |
| $R^a$ | hydrogen | (all) |
| $R^b$ | hydrogen | (all) |
| $R^c$ | hydrogen | (all) |

*The phrase "tested compound" indicates that the compound was tested in at least one of the three assays referenced and described above.

However, the enablement provided by the specification is not limited to these data. A person of ordinary skill in the art would appreciate that the exemplification with respect to these

specific operative compounds, provides guidance regarding structure-activity relationships (SAR) that limits the experimentation required to identify and/or characterize additional related compounds. The specification also provides substantial guidance as to how to evaluate compounds of the claimed compositions. For example, the Examiner is directed to paragraph [0368], which describes methods of evaluating the ability of compounds of the claimed compositions to inhibit cell migration. In particular, the Examiner is directed to the statement that "***The study helped provide a broad SAR picture with respect to migrastatin analogs.***" Structure-activity relationship (SAR) trends are further discussed in, *e.g.,* paragraph [0405].

Applicant respectfully reminds the Examiner that it is required that the Examiner take as true the data provided in the specification absent a reason to doubt these data. The Examiner provides no reason to doubt the assertions made in the specification regarding the activity and utility of the claimed compositions. Applicant emphasizes that case law holds that:

> "in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)..A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is *a reason to doubt* the objective truth of the statements contained therein which must be relied on for enabling support." (see MPEP 2164.04, emphasis added)

Separately, with respect to the legal standard set forth in *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984), *i.e.*, the requirement that the specification teach those skilled in the art how to make and use the invention without undue experimentation, Applicant submits that Applicant has fully complied with this standard. To the extent a person skilled in the art would need to test the utility of individual migrastatin analogs within the claimed genus, such testing would be routine, not undue.

As quoted in MPEP § 2164.06:

> "[t]he [undue experimentation] test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, ***or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed***." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214, 217-19 (CCPA 1976)). (emphasis added)

In regards to testing compounds of the claimed compositions, Applicant directs the Examiner to paragraphs [0254]-[0258], which disclose, *inter alia*, high-throughput methods for

"identifying Migrastatin analogs useful in the preparation of pharmaceutical compositions for the treatment of metastasis-related disorders." Applicant further describes how compounds of the claimed compositions can be administered in accordance with the claims (see *e.g.,* paragraphs [0260]-[0265], [0279]-[0280], and [0306]-[0308]). Paragraphs [0307] and [0308] on page 133 of the specification provide dosage ranges for treating, *inter alia*, cancer and/or disorders associated with metastasis. Besides, MPEP § 2164.01(c) states that:

> "[...] it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, ***based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph***." (emphasis added)

Applicant notes that the above-referenced specification paragraphs are merely exemplary. In view of the specification as a whole, and especially the above-referenced paragraphs, Applicant submits that experimentation would not be "undue". Rather, while it may be time-consuming, it would be routine. The Examiner is respectfully reminded that "[An] extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni,* 561 F.2d at 224, 195 USPQ at 153.

In addition to the above-referenced data and disclosures, the specification also clearly states that its teachings are applicable to other analogs (see, *e.g.,* paragraph [0328] (page 141) and paragraphs [0332]-[0333] (pages 142-143)). In this context, MPEP § 2164.02 states that:

> "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus ***only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation***."

Finally, Applicant takes this opportunity to remind the Examiner that the present invention was not made in a vacuum. It was made in the context of significant information about *migrastatin*, which is a natural compound, *known in the art* prior to the filing of the present application. Migrastatin was known to be useful, among other things, ***to inhibit both migration and anchorage-independent growth of human tumor cells*** (see, *e.g.,* paragraph [0004] (page 1) and paragraphs [0324] to [0326] (pages 138-139)). A number of structural homologs of migrastatin were known in the art at the time of filing and had been reported to exhibit anti-tumor activity *in vivo* and *in vitro* (see, *e.g.,* paragraph [0325] (page 139) and references cited therein).

With respect to the Examiner's remark on page 5 of the Office Action that "[...] the art of using compounds to treat tumors is highly unpredictable [...]. In nearly every case, the skilled artisan could not predict *a priori* whether a given compound would affect a tumor," Applicant submits that this level of certainty is not required by law. Applicant reminds the Examiner that:

> "The presence of inoperative embodiments within the scope of a claim does not necessarily render the claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort ***than is normally required in the art***." *Atlas Powder Co. v. E. I. duPont de Nemous & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Circ. 1984) (emphasis added)

Given the state of the art and the level of guidance provided by the specification, Applicant submits that the identification of operative or inoperative examples would require no more effort than is normally required in the art. For the reasons discussed above, experimentation would be routine and not undue.

Thus, in view of Applicant's amendments to the claims, and in light of the provided data establishing the activity of compounds of the claimed compositions, the understanding in the art of the anti-metastatic activities of migrastatin and analogs thereof, the ample guidance provided by the specification to make and use compounds of the claimed compositions, and the reasonable assertions in the specification, Applicant submits that the present invention does indeed reasonably provide enablement for the asserted utility of the entirety of the present claim scope. Therefore, this rejection should be removed.

## II. **Rejoinder**

Should the Examiner deem that there is allowable subject matter in the present claims as amended, Applicant respectfully requests that the Examiner consider the following comments. MPEP §821.04 states:

> "The propriety of a restriction requirement should be reconsidered when all the claims directed to the elected invention are in condition for allowance, and the nonelected invention(s) should be considered for rejoinder. Rejoinder involves withdrawal of a restriction requirement between an allowable elected invention and a nonelected invention and examination of the formerly nonelected invention on the merits."

Applicant submits that because claim 1 (*i.e.,* the elected invention) is in condition for allowance, all dependent claims therefrom are also patentable and allowable. Applicant respectfully requests that the claims deemed "non-elected" (*i.e.,* claims 28-29, and 31) are now appropriate subject matter for rejoinder. Therefore, Applicant respectfully requests that examination on the merits proceed accordingly, *i.e.,* if there is no art that anticipates or renders obvious the elected species, then Applicant requests that the search of the claim be extended.

**Conclusion**

In light of the above Remarks, Applicant invites the Examiner to contact the undersigned, Brenda Herschbach Jarrell, at (617) 248-5175, with any questions pertaining to the above-identified application in order to expedite prosecution of this case.

Respectfully submitted,

**Dated: August 2, 2010**

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